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This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

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☐ *Additional inventors are being named on the ____ separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

HCV Drugs

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages* 27 ☐ CD(s), Number

☐ Drawing(s) *Number of Sheets* ☐ Other (specify)

☐ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☒ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check or money order is enclosed to cover the filing fees — FILING FEE AMOUNT ($)

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: ____.

[Page 1 of 1]

Respectfully submitted,

SIGNATURE _____ Date 06/20/03

TYPED or PRINTED NAME Mark DeLuca REGISTRATION NO. *(if appropriate)* 33,229

TELEPHONE 215-665-5592 Docket Number: VGX0002-001

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop Provisional Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Viral Genomix Patent Filing: VGX IP-002

Inventor: Jong Joseph Kim

Initial Title: HCV Drugs

1) Drugs which disrupt mov34, a member of EIF3 complex can be used as a treatment for HCV infection.
2) EIF3/viral IRES/40S complex is important for viral protein translation of hepatitis C virus (HCV) and other viruses.
3) GRII antagonist drugs, including Mifepristone, can target and disrupt function/structure of mov34, a member of EIF3 complex.
4) Use of other drug compounds to block/inhibit EIF3/mov34 (antisense, antibodies, inhibitory RNA)
5) Delivery of drugs via patch, sustained release, and subdermal delivery.

EIF3 is important for viral protein translation

Eukaryotic cells and their viruses have evolved at least two mechanisms for recruiting and positioning ribosomes at the start sites for translation of RNA messages. The primary mechanism involves recognition of a 7-methyl guanosine cap on the 5' terminus of the mRNA by a set of canonical initiation factors that recruit the 43S particle—including the 40S ribosomal subunit and eukaryotic initiation factor 3 (eIF3)—forming the 48S preinitiation complex (Merrick & Hershey, 1996; Pain, 1996; Sachs et al., 1997). Alternatively, numerous viruses and some eukaryotic mRNAs utilize a cap-independent pathway in which an RNA element, the internal ribosome entry site (IRES), drives preinitiation complex formation by positioning the ribosome on the message, either at or just upstream of the start site. In hepatitis C virus (HCV), the major infectious agent leading to non-A, non-B hepatitis, the minimum IRES includes nearly the entire 5' untranslated region (UTR) of the message (for review, see Rijnbrand & Lemon, 2000). The secondary structure of the HCV IRES RNA, one of the most conserved regions of the entire viral genome, is critical for translation initiation, and is similar to that of the related pestiviruses and GB virus B (Brown et al., 1992; Wang et al., 1994, 1995; Le et al., 1995; Rijnbrand et al., 1995; Honda et al., 1996a, 1996b, 1999; Pickering et al.,1997; Varaklioti et al., 1998; Psaridi et al., 1999; Tang et al., 1999).

The 341-nucleotide 5' non-translated region is the most conserved part of the hepatitis C virus (HCV) genome. It contains a highly structured internal ribosomal entry site (IRES) that mediates cap-independent initiation of translation of the viral polyprotein by a mechanism that is unprecedented in eukaryotes. The first step in translation initiation is assembly of eukaryotic initiation factor (eIF) 3, eIF2, GTP, initiator tRNA and a 40S ribosomal subunit into a 43S preinitiation complex (Buratti et al., 1998, Kieft et al., 2001). The HCV IRES recruits this complex and directs its precise attachment at the

initiation codon to form a 48S complex in a process that does not involve eIFs 4A, 4B or 4F. The IRES contains sites that bind independently with the eIF3 and 40S subunit components of 43S complexes, and structural determinants that ensure the correct spatial orientation of these binding sites so that the 48S complex assembles precisely at the initiation codon.

HCV IRES RNA adopts a specific three-dimensional fold in the presence of physiological concentrations of metal ions (Kieftet al., 1999). Rather than forming a tightly packed globular structure, the RNA helices extend from two folded helical junctions, suggesting that the IRES RNA acts as a structural scaffold in which specifically placed recognition sites recruit the translational machinery. This is supported by the observation that eIF3 and the 40S ribosomal subunit, the two largest components of the 43S particle, bind directly to the HCV IRES RNA (Pestova et al., 1998). Unlike IRESs found in some other RNA viruses, such as poliovirus, the IRES RNA•40S•eIF3 ternary pre-initiation complex forms without the involvement of other cellular factors (Pestova et al., 1998). Although several other proteins appear to interact with the HCVIRES RNA, they are not required for 43S binding to the IRES (Ali & Siddiqui, 1995, 1997; Yen et al., 1995; Hahmet al., 1998; Fukushi et al., 1999).

IRES/EIF/40S complexes have been reported to be important for other RNA viruses. Flavivruses [such as GBV-B, GBV-C, Japanese Encephalovirus (JEV) and West Nile Virus (WNV)] (Malancha & Sudhanshu, 2000, Blackwell & Brinton, 2000) as well as pestiviruses [such as classical swine fever virus (CSFV), border disease virus (BDV), and bovine viral disease virus (BVDV)] (Sizova et al, 1998, Pestova et al., 1998, Fletcher et al., 2002) and picornoviruses [such as poliovirus, Foot and mouth disease virus (FMDV) and encephalomyocarditis virus (EMCV)] (Jang et al., 1988, Pelletier & Sonenberg, 1988) and calicivirus [such as the Norwalk virus] (Daughenbaugh et al. 2003). Similar ribosomal binding sites on coronaviruses have been reported to be important for RNA translation, replication, or transcription (O'Connor & Brian, 2000, Raman et al, 2003).

GRII antagonist drugs can disrupt function/structure of mov34, a member of EIF3 complex

Using a yeast two-hybrid system, the cDNA of a Vpr-interacting cellular factor, termed human Vpr Interacting Protein (hVIP/mov34) was cloned (Mahalingam et al., 1998) hVIP/mov34 has complete homology with a reported member of the eIF3 complex (Asano et al., 1997). eIF3 is a large multimeric complex that regulates transcriptional events and is essential for G1/S and G2/M phase progression through the cell cycle. hVIP is thought to be a GR-responsive protein. Experimental results strongly suggest that hVIP is associated with the activated glucocorticoid receptor complex.

Glucocorticoids regulate diverse functions and are important to maintain central nervous system, cardiovascular, metabolic, and immune homeostasis. They also exert anti-inflammatory and immunosuppressive effects, which have made them invaluable therapeutic agents in numerous diseases (Chrousos, 1995). The actions of these hormones are mediated by their specific intracellular receptors, such as the GR. Several host co-activators of the GR have been described that directly interact with GR and

components of the transcription initiation complex to enhance the glucocorticoid signal to the transcription machinery (Shibata et al., 1997).

The GR is the prototypic member of the translocating class of steroid receptors that are ubiquitously expressed in almost all human tissues and organs. Unliganded GR is found in the cytoplasm and moves rapidly into the nucleus in response to hormone stimulation (Htun et al., 1996, McNally et al., 2000). GR interacts in the cytoplasm with a complex array of chaperone proteins, including HSP90 and HSP70, and ligand-dependent displacement of these proteins is thought to be intimately involved in the translocation process (Bamberger et al., 1996, Beato et al., 1996). Both GR and hVIP are known Vpr ligands. Steroid hormone receptor antagonists such as mifepristone prevent the GR from moving into the nucleus in response to appropriate stimulation. In addition, mifepristone blocks the Vpr-induced nuclear entry of hVIP. HVIP had been reported as a potential Vpr ligand and demonstrated its role in cell cycle regulation as antisense of this gene induced cell cycle arrest at the G2/M phase (Mahalingam et al., 1998).

Glucocorticoids have been demonstrated to mimic the effects of Vpr; mifepristone has been shown to revert these effects of Vpr (Ayyavoo et al., 1997, Ayyavoo et al., 2002, Kino et al., 1999, Sherman et al., 2000). Moreover, mifepristone has been shown to block the nuclear translocation of hVIP induced by Vpr in cells. This result clearly demonstrates that mifepristone inhibits the translocation of hVIP induced by the expression of Vpr and strongly suggested that mifepristone and other GR antagonists can directly effect hVIP/mov34. In addition, these results implicate the use of other drug compounds to block/inhibit EIF3/mov34 (antisense, antibodies, inhibitory RNA) as a potential treatment for viral pathogens like Hepatitis C virus.

SUMMARY OF THE INVENTION

The present invention further relates to pharmaceutical composition comprising: a pharmaceutically acceptable carrier or diluent; and, a compound that inhibits HCV replication, the compound having a structure selected from the group consisting of mifepristone, Formula D1, Formula D2, Formula D3, Formula D4, Formula D5, and pharmaceutically acceptable salts thereof.

The present invention further relates to methods of treating an individual who has been infected with HCV. The method comprise the step of administering to the individual an amount of a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent, and, a compound that inhibits HCV replication having a structure selected from the group consisting of mifepristone, Formula D1, Formula D2, Formula D3, Formula D4, Formula D5, and pharmaceutically acceptable salts thereof effective to inhibit HCV replication in the individuals.

The present invention further relates to methods of preventing HCV infection in an individual at an elevated risk of becoming HCV infected. The method comprise the step of administering to the individual a prophylactically effective amount of a pharmaceutical composition that comprises a pharmaceutically acceptable carrier or diluent, and, a compound that inhibits HCV replication having a structure selected from the group consisting of mifepristone, Formula D1, Formula D2, Formula D3, Formula D4, Formula D5, and pharmaceutically acceptable salts thereof effective to inhibit HCV replication.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention provides pharmaceutical compositions comprising a compound having a structure selected from the group consisting of mifepristone, Formula D1, Formula D2, Formula D3, Formula D4, Formula D5, and pharmaceutically acceptable salts thereof. The present invention provides methods of treating individuals infected with HCV by administering to them a therapeutically effective amount of such compositions. The present invention further provides methods of preventing HCV infection in individuals exposed to HCV, by administering to them a prophylactically effective amount of such compositions.

The present invention is useful to therapeutically treat an individual identified as infected with HCV in order to eliminate, reduce or stabilize viral titer. The present invention is useful to prophylactically treat a high risk individual from becoming infected with HCV.

The compounds of the invention may act as steroid hormone receptor antagonists that interactively blocks Rip-1/mov34, alone or in association with one or more steroid receptors, or other components, or one or more steroid receptors alone, preventing or inhibiting formation and translocation of the Rip-1 and/or steroid receptor or other EIF component complex.

As used herein, the term "high risk individual" is meant to refer to an individual who is suspected of having been exposed to the HCV virus. Such individuals include health care or other individuals who may have accidently exchanged blood with an HVV-infected individual, such as through an accidental needle stick, injuries that occur during emergency medical care, rescue or arrest and unprotected sexual contact. High risk

individuals can be treated prophylactically before any detection of HVV infection can be made.

As used herein, the term "therapeutically effective amount" is meant to refer to an amount of a compound which produces a medicinal effect observed as reduction or reverse in viral titer when a therapeutically effective amount of a compound is administered to an individual who is infected with HCV. Therapeutically effective amounts are typically determined by the effect they have compared to the effect observed when a composition which includes no active ingredient is administered to a similarly situated individual.

As used herein, the term "prophylactically effective amount" is meant to refer to an amount of a compound which produces a medicinal effect observed as the prevention of HCV infection in an individual when a prophylactically effective amount of a compound is administered to a high risk individual. Prophylactically effective amounts are typically determined by the effect they have compared to the effect observed when a composition which includes no active ingredient is administered to a similarly situated individual.

The invention provides novel pharmaceutical compositions comprising antiviral compounds that are inhibitors of HCV replication. The antiviral compounds included in the pharmaceutical compositions of the present invention have a formula selected from the group consisting of mifepristone, Formula D1, Formula D2, Formula D3, Formula D4, Formula D5, as set forth below, or a pharmaceutically acceptable salt thereof. The invention provides novel pharmaceutical compositions comprising antiviral compositions that inhibit HCV replication. In some preferred embodiments, the HCV replication inhibitor in the pharmaceutical compositions of the present invention has a formula of mifepristone as set forth in the section below entitled Formulae. In some preferred embodiments, the HCV replication inhibitor in the pharmaceutical compositions of the present invention has a formula of Formula 1 as set forth in the section below entitled Formulae. In some preferred embodiments, the HCV replication inhibitor in the pharmaceutical compositions of the present invention has a formula of Formula 2 as set forth in the section below entitled Formulae. In some preferred embodiments, the HCV replication inhibitor in the pharmaceutical compositions of the present invention has a formula of Formula 3 as set forth in the section below entitled Formulae. In some preferred embodiments, the HCV replication inhibitor in the pharmaceutical compositions of the present invention has a formula of Formula 4 as set forth in the section below entitled Formulae. In some preferred embodiments, the HCV replication inhibitor in the pharmaceutical compositions of the present invention has a formula of Formula 5 as set forth in the section below entitled Formulae.

In some embodiments the method of the invention additionally includes the use of the HCV replication inhibitor compositions of the invention in combination with other methodologies to treat HCV infection. In some embodiments, the HCV replication inhibitor is administered in conjunction with other antiviral agents such as acyclovir, ganciclovir, foscarnet, lamivudine, ribavirin, interferon alpha-2a, interferon alpha-2b, peginterferon alfa-2a, and peginterferon alfa-2b.

The pharmaceutical compositions comprising HCV replication inhibitor compositions of the present invention may be administered by any means that enables the active agent to reach the agent's site of action in the body of the individual. Pharmaceutical compositions of the present invention may be administered by conventional routes of pharmaceutical administration. Pharmaceutical compositions may be administered parenterally, i.e. intravenous, subcutaneous, intramuscular, subdermally, transdermally. In some embodiments, the pharmaceutical compositions are administered orally. Pharmaceutical compositions are administered to the individual for a length of time effective to eliminate, reduce or stabilize viral titer. When used prophylactically, Pharmaceutical compositions are administered to the individual for a length of time during which monitoring for evidence of infection continues.

Pharmaceutical compositions of the present invention may be administered either as individual therapeutic agents or in combination with other therapeutic agents. They can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

Dosage varies depending upon known factors such as the pharmacodynamic characteristics of the particular agent, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms, kind of concurrent treatment, frequency of treatment, and the effect desired. Usually a daily dosage of active ingredient can be about 0.001 to 1 grams per kilogram of body weight, in some embodiments about 0.1 to 100 milligrams per kilogram of body weight. Ordinarily dosages are in the range of 0.5 to 50 milligrams per kilogram of body weight, and preferably 1 to 10 milligrams per kilogram per day. In some embodiments, the pharmaceutical compositions are given in divided doses 1 to 6 times a day or in sustained release form is effective to obtain desired results.

Dosage forms (composition) suitable for internal administration generally contain from about 1 milligram to about 500 milligrams of active ingredient per unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95 by weight based on the total weight of the composition. Generally, multiple administrations are performed.

Pharmaceutical compositions may be formulated by one having ordinary skill in the art with compositions selected depending upon the chosen mode of administration. Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences*, A. Osol, a standard reference text in this field, which is incorporated herein by reference.

For parenteral administration, the compound can be formulated as a solution, suspension, emulsion or lyophilized powder in association with a pharmaceutically acceptable parenteral vehicle. Examples of such vehicles are water, saline, Ringer's solution, dextrose solution, and 5% human serum albumin. Liposomes and nonaqueous vehicles such as fixed oils may also be used. The vehicle or lyophilized powder may contain additives that maintain isotonicity (e.g., sodium chloride, mannitol) and chemical stability

(e.g., buffers and preservatives). The formulation is sterilized by commonly used techniques. In some embodiments, a parenteral composition suitable for administration by injection is prepared by dissolving 1.5% by weight of active ingredient in 0.9% sodium chloride solution.

According to some embodiments of the present invention, the composition is administered to tissue of an individual by topically or by lavage. The compounds may be formulated as a cream, ointment, salve, douche, suppository or solution for topical administration or irrigation. The compounds may be formulated as a transdermal patch or subdermal implants. Formulations for such routes administration of pharmaceutical compositions are well known. Generally, additives for isotonicity can include sodium chloride, dextrose, mannitol, sorbitol and lactose.

In some cases, isotonic solutions such as phosphate buffered saline are used. Stabilizers include gelatin and albumin. In some embodiments, a vasoconstriction agent is added to the formulation. The pharmaceutical preparations according to the present invention are preferably provided sterile and pyrogen free. The pharmaceutical preparations according to the present invention which are to be used as injectables are provided sterile, pyrogen free and particulate free.

A pharmaceutically acceptable formulation will provide the active ingredient(s) in proper physical form together with such excipients, diluents, stabilizers, preservatives and other ingredients as are appropriate to the nature and composition of the dosage form and the properties of the drug ingredient(s) in the formulation environment and drug delivery system.

In some embodiments, the invention relates to methods of treating patients suffering from HCV infection. In some embodiments, the invention relates to methods of preventing HCV infection in high risk individuals.

According to some embodiments of the invention, the patient is treated with other antiviral therapy in conjunction the administration of pharmaceutical compositions according to the invention. The use of multiple therapeutic approaches provides the patient with a broader based intervention.

According to some aspects of the present invention, in combination with administration of the composition that comprises the HCV replication inhibitor, the individual is also administered another agent. In some embodiments, in combination with administration of the composition, the individual additionally receives compositions that comprises acyclovir, ganciclovir, foscarnet, lamivudine, ribavirin, interferon alpha-2a, interferon alpha-2b, peginterferon alfa-2a, and peginterferon alfa-2b.

Other antivirals may also be used delivered according to standard protocols using standard agents, dosages and regimens. In some embodiments, the pharmaceutical compositions contain one or more of the compounds selected from the group consisting of mifepristone, Formula D1, Formula D2, Formula D3, Formula D4, Formula D5, and

pharmaceutically acceptable salts thereof. In some embodiments, the pharmaceutical compositions contain one or more of the compounds selected from the group consisting of mifepristone, Formula D1, Formula D2, Formula D3, Formula D4, Formula D5, and pharmaceutically acceptable salts thereof and at least one additional antiviral selected from the group consisting of: acyclovir, ganciclovir, foscarnet, lamivudine, ribavirin, interferon alpha-2a, interferon alpha-2b, peginterferon alfa-2a, and peginterferon alfa-2b, together with a pharmaceutically acceptable carrier.

The pharmaceutical compositions according to the present invention may be administered as a single doses or in multiple doses. The pharmaceutical compositions of the present invention may be administered either as individual therapeutic agents or in combination with other therapeutic agents. The treatments of the present invention may be combined with conventional therapies, which may be administered sequentially or simultaneously.

In addition to treating HCV-infected individual, the present invention relates to methods of preventing HCV infection in high risk individuals who, for example, are suspected of having been exposed to the virus.

Additionally, the present invention is particularly useful to prevent recurrence of infection in patients who have been previously diagnosed as HCV positive but show no indication of infection.

Those having ordinary skill in the art can readily identify high risk individuals. Healthcare workers come into contact with infected blood and suffer needle sticks from syringes used on HCV infected individuals. Surgeons cut themselves during surgery. Lab workers, dentists and dental technicians come into contact with infected blood as do emergency medical and rescue workers and law enforcement officers. Individuals involved in athletics and sexually active individuals can also become exposed to the virus. Once any person comes into contact with infected blood, that individual is at an elevated risk of infection.

The present invention is not limited to any particular theory or mechanism of action and while it is currently believed that the compounds identified herein operate through blocking the steroid hormone receptor complex that comprises Rip-1/mov34, such explanation of the mechanism of action is not intended to limit the invention. The present invention is further illustrated by the following examples, which are not intended to be limiting in any way.

CLAIMS

1. A pharmaceutical composition comprising: a pharmaceutically acceptable carrier or diluent; and a compound having a structure selected from glucocorticoid receptor II antagonists.

2. A pharmaceutical composition comprising: a pharmaceutically acceptable carrier or diluent; and a compound having a structure selected from the group consisting of mifepristone, Formula D1-D18, and pharmaceutically acceptable salts thereof.

3. A pharmaceutical composition comprising: a pharmaceutically acceptable carrier or diluent; and antisense, inhibitory RNA, and peptide mimetic compounds targeting EIF/mov34 and/or GR II.

4. The pharmaceutical composition of claims 1-2 comprising mifepristone.

5. The pharmaceutical composition of claims 1-2 comprising Compound D1.

6. The pharmaceutical composition of claims 1-2 comprising Compound D2.

7. The pharmaceutical composition of claims 1-2 comprising Compound D3.

8. The pharmaceutical composition of claims 1-2 comprising Compound D4.

9. The pharmaceutical composition of claims 1-2 comprising Composition D5.

10. The pharmaceutical composition of claims 1-2 comprising Composition D6.

11. The pharmaceutical composition of claims 1-2 comprising Composition D7.

12. The pharmaceutical composition of claims 1-2 comprising Composition D8.

13. The pharmaceutical composition of claims 1-2 comprising Composition D9.

14. The pharmaceutical composition of claims 1-2 comprising Composition D10.

15. The pharmaceutical composition of claims 1-2 comprising Composition D11.

16. The pharmaceutical composition of claims 1-2 comprising Composition D12.

17. The pharmaceutical composition of claims 1-2 comprising Composition D13.

18. The pharmaceutical composition of claims 1-2 comprising Composition D14.

19. The pharmaceutical composition of claims 1-2 comprising Composition D15.

20. The pharmaceutical composition of claims 1-2 comprising Composition D16.

21. The pharmaceutical composition of claims 1-2 comprising Composition D17.

22. The pharmaceutical composition of claims 1-2 comprising Composition D18.

23. The pharmaceutical composition of claims 4-22 further comprising a compound having a structure selected from the group consisting: acyclovir, ganciclovir, foscarnet, lamivudine, ribavirin, interferon alpha-2a, interferon alpha-2b, peginterferon alfa-2a, and peginterferon alfa-2b.

24. The pharmaceutical composition of claims 1-22 comprising: a pharmaceutically acceptable carrier or diluent; and, a compound having a structure selected from the group consisting of mifepristone, Formulas D1-D18, and pharmaceutically acceptable salts thereof and further comprising a compound having a structure selected from the group consisting: acyclovir, ganciclovir, foscarnet, lamivudine, ribavirin, interferon alpha-2a, interferon alpha-2b, peginterferon alfa-2a, and peginterferon alfa-2b.

25. A method of treating an individual who is infected with HCV comprising the step of administering to said individual a therapeutically effective amount of a composition according to claims 1-22.

26. A method of preventing HCV infection in an individual identified as being a high risk individual, the method comprising the step of administering to said individual a prophylactically effective amount of a composition according to claims 1-22.

27. A method of treating an individual who is infected with WNV comprising the step of administering to said individual a therapeutically effective amount of a composition according to claims 1-22.

28. A method of preventing WNV infection in an individual identified as being a high risk individual, the method comprising the step of administering to said individual a prophylactically effective amount of a composition according to claims 1-22.

29. A method of treating an individual who is infected with JEV comprising the step of administering to said individual a therapeutically effective amount of a composition according to claims 1-22.

30. A method of preventing JEV infection in an individual identified as being a high risk individual, the method comprising the step of administering to said individual a prophylactically effective amount of a composition according to claims 1-22.

31. A method of treating an individual who is infected with poliovirus comprising the step of administering to said individual a therapeutically effective amount of a composition according to claims 1-22.

32. A method of preventing poliovirus infection in an individual identified as being a high risk individual, the method comprising the step of administering to said individual a prophylactically effective amount of a composition according to claims 1-22.

33. A method of treating an individual who is infected with EMCV comprising the step of administering to said individual a therapeutically effective amount of a composition according to claims 1-22.

34. A method of preventing EMCV infection in an individual identified as being a high risk individual, the method comprising the step of administering to said individual a prophylactically effective amount of a composition according to claims 1-22.

35. A method of treating an individual who is infected with CSFV comprising the step of administering to said individual a therapeutically effective amount of a composition according to claims 1-22.

36. A method of preventing CSFV infection in an individual identified as being a high risk individual, the method comprising the step of administering to said individual a prophylactically effective amount of a composition according to claims 1-22.

37. A method of treating an individual who is infected with BVDV comprising the step of administering to said individual a therapeutically effective amount of a composition according to claims 1-22.

38. A method of preventing BVDV infection in an individual identified as being a high risk individual, the method comprising the step of administering to said individual a prophylactically effective amount of a composition according to claims 1-22.

39. A method of treating an individual who is infected with GBV-B comprising the step of administering to said individual a therapeutically effective amount of a composition according to claims 1-22.

40. A method of preventing GBV-B infection in an individual identified as being a high risk individual, the method comprising the step of administering to said individual a prophylactically effective amount of a composition according to claims 1-22.

41. A method of treating an individual who is infected with GBV-C comprising the step of administering to said individual a therapeutically effective amount of a composition according to claims 1-22.

42. A method of preventing GBV-C infection in an individual identified as being a high risk individual, the method comprising the step of administering to said individual a prophylactically effective amount of a composition according to claims 1-22.

43. A method of treating an individual who is infected with human coronavirus comprising the step of administering to said individual a therapeutically effective amount of a composition according to claims 1-22.

44. A method of preventing human coronavirus infection in an individual identified as being a high risk individual, the method comprising the step of administering to said individual a prophylactically effective amount of a composition according to claims 1-22.

45. A method of treating an individual who is infected with Norwalk virus comprising the step of administering to said individual a therapeutically effective amount of a composition according to claims 1-22.

46. A method of preventing Norwalk virus infection in an individual identified as being a high risk individual, the method comprising the step of administering to said individual a prophylactically effective amount of a composition according to claims 1-22.

47. A method of treating an individual who is infected with human RNA virus comprising the step of administering to said individual a therapeutically effective amount of a composition according to claims 1-22.

48. A method of preventing human RNA virus infection in an individual identified as being a high risk individual, the method comprising the step of administering to said individual a prophylactically effective amount of a composition according to claims 1-22.

Transdermal Drug Delivery

The skin is the largest and most accessible organ of the human body. The permeability of the skin and its ability to deliver drugs to the blood circulation makes it an ideal drug delivery route. Transdermal drug delivery is an increasingly important method of drug administration. Transdermal drug delivery devices typically involve a carrier (such as a liquid, gel, or solid matrix, or a pressure sensitive adhesive) into which the drug to be delivered is incorporated. The drug-containing carrier is then placed on the skin and the drug, along with any adjuvants and excipients, is delivered to the skin.

Typically the portions of the carrier that are not in contact with the skin are covered by a backing. The backing serves to protect the carrier (and the components contained in the carrier, including the drug) from the environment and prevents loss of the ingredients of the drug delivery device to the environment. Backing materials that have found use in transdermal drug delivery devices include metal foils, metalized plastic films, and single layered and multilayered polymeric films.

Transdermal drug delivery utilizes the skin for the delivery of the drug molecules from the surface of the skin, through its layers, to the circulatory system. The transdermal drug delivery technology comprises of a controlling system that regulates the rate of drug delivery to the skin, and another that uses the skin to control the absorption rate.

Transdermal drug delivery occurs in two ways: passive and active transdermal delivery. Passive systems allow the drug to diffuse through the skin into the bloodstream using a simple concentration gradient as a driving force. Active delivery system requires a physical force to facilitate the movement of drug molecules across the skin.

The first transdermal patch was introduced in 1981. Subsequently, the applications of transdermal drug delivery have been expanded to include more products in multiple therapeutic areas. Numerous kinds of medications have been administered through the use of a patch, notably scopolamine for preventing motion sickness, nicotine derivatives intended to discourage an addicted smoker from continuing the smoking habit and estrogen hormones.

Prior art teaches us methods to load and deliver drugs via transdermal routes. U.S. Patent No. 5,223,261 describes a loading and using a transdermal delivery system for delivering estradiol. U.S. Patent No. 5,380,760 describes a transdermal delivery system for delivering prostaglandin. U.S. Patent No. 5,702,720 describes a transdermal delivery system for delivering flurbiprofen. U.S. Patent No. 6,132,760 describes a transdermal delivery system for delivering testosterone.

The amount of drug that constitutes a therapeutically effective amount varies according to the condition being treated, any drugs being coadministered with the drug, desired duration of treatment, the surface area and location of the skin over which the device is to be placed, and the selection of adjuvant and other components of the transdermal delivery device. Accordingly, it is not practical to enumerate particular preferred amounts but such can be readily determined by those skilled in the art with due consideration of these and

other appropriate factors. Generally, however, the drug is present in the adhesive layer in an amount of about 2 to about 9 percent, preferably about 2.5 to about 6.5 percent, by weight based on the total weight of the adhesive layer. A device of the invention preferably contains a therapeutically effective amount of the drug dissolved in the adhesive layer.

The adhesive layer of the device of the invention also comprises one or more polymers, typically one or more copolymers. The polymer(s) utilized in the practice of the invention should be substantially chemically inert to the drug, and is preferably a pressure sensitive skin adhesive. Examples of suitable types of adhesives include acrylates, natural and synthetic rubbers, polysiloxanes, polyurethanes, and other pressure sensitive skin adhesives known in the art, either alone or in combination. Preferably the adhesive is an acrylate copolymer.

Delivery of Mifepristone/GR II Antagonists via Transdermal Patch

The present invention provides transdermal drug delivery devices containing mifepristone, Compositions D1-D5 or other GRII antagonists (Drugs). The drug is present in the adhesive layer in a therapeutically effective amount, i.e., an amount effective to allow the device to deliver sufficient amount of the drug to achieve a desired therapeutic result in the treatment of a condition.

A delivery of mifepristone via a transdermal patch would reduce the number of drugs a patient must take orally and improve compliance. The transdermal drug delivery would be most appropriate in cases where low systemic and steady state drug concentration is desirable. This delivery method could enhance patient compliance and could reduce the effects of potential drug toxicities.

There are several advantages of delivering anti-viral drugs via transdermal delivery systems. Transdermal drug delivery is not subjected to first-pass effect and does not cause frequent drug concentration alterations as compared to the drugs delivered through the oral route. This reduces the required dose in comparison to the oral drug delivery. Medications delivered via skin patches avoid liver metabolism and hence allow for lower doses of medication. It also avoids potential toxicity of the drug to the liver. The transdermal drug delivery also offers the flexibility of terminating the drug administration by simply removing the patch from the skin. This delivery system releases a controlled amount of a drug over a long period of time. Transdermal patch systems exhibit slow controlled drug release and absorption and the plasma drug concentration does not vary significantly over time. This delivery method would enhance patient compliance and thereby a reduction of drug resistant viruses as well as reduce the effects of potential drug toxicities.

Subdermal Drug Delivery (Implantable Devices)

A principal advantage of employing sustained-release compositions is that many therapeutic agents would otherwise be rapidly metabolized or cleared from the patient's

system necessitating frequent administration of the drug to maintain a therapeutically effective concentration.

Accordingly, a variety of sustained release devices have been designed for oral, rectal and subcutaneous administration. "Matrix" type devices typically consist of an active compound dispersed in a matrix of carrier material which may be either porous or non-porous, solid or semi-solid, and permeable or impermeable to the active compound. These devices are rather easily prepared; however, they are not suitable for administering some pharmacologically active compounds. In addition, the rate of release of the active compound decreases with time. "Reservoir" type devices consist of a central reservoir of active compound surrounded by a rate controlling membrane (rcm). The rcm is generally a porous or a non-porous material which is non-biodegradable. In the case of the transdermal devices of this type, to maintain an effective concentration of active compound, the rate controlling membrane must have a large surface area. Thus, a common disadvantage of these devices is that their large size makes administration quite inconvenient. Other sustained release devices are hybrid-type devices which contain a matrix core surrounded by a rcm. Yet other devices are mechanical in nature, and include active compound-filled electrical or osmotic pumps.

The subdermally implantable devices of the present invention can be prepared in a variety of sizes and shapes to accommodate such factors as the specific implantation site and the desired release rate of the drug. In a preferred embodiment wherein the drug is a contraceptive agent, the device is substantially cylindrical in shape having a preferred overall length of from about 4.2 cm to about 4.6 cm, and a preferred overall diameter of from about 2.3 mm to about 2.7 mm. In such a case, the central core is rod-shaped, and has a preferred length of from about 3.8 cm to about 4.2 cm, and a preferred diameter of from about 2.0 mm to about 2.2 mm. These dimensions can be modified depending upon such factors as the implantation site and method of implantation, the subject, the condition to be treated, the drug, and the desired release rate of the drug, etc. For example, the length of the implantable device can be varied to deliver different amounts of the drug.

Prior art teaches us methods to load and deliver drugs via subdermal routes. The subdermally implantable devices according to the present invention can be easily fabricated in accordance with standard techniques. Once the drug is mixed with the matrix material to achieve a substantially uniform dispersion, the desired shape of the resultant dispersion is achieved by molding, casting extrusion, or other appropriate process. When the matrix material contains polymers such as silicone elastomers, an additional curing step may be necessary. The intermediate layer is then applied to the thus-shaped matrix, e.g., by swelling, coating or laminating according to known techniques, a polymeric tube in water and then placing it over the matrix and allowing the polymer to dry in place, or by mechanical lapping. The outer layer can likewise be applied in a variety of ways such as by mechanical stretching, swelling or dipping. See, for example, U.S. Pat. Nos. 3,832,252, 3,854,480 and 4,957,119. U.S. Patent No. 5,756,115 describes a loading and using a subdermal delivery system for delivering contraceptives. The dimensions of the implant are also determined on the basis of the

implantation method. The devices of the present invention can be implanted into a subject in accordance with standard procedures.

The present invention provides subdermal drug delivery devices containing mifepristone, Compositions D1-D5 or other GRII antagonists (Drugs). The drug is present in the implantable devices in a therapeutically effective amount, i.e., an amount effective to allow the device to deliver sufficient amount of the drug to achieve a desired therapeutic result in the treatment of a condition.

Sustained and Controlled Release Drug Delivery

To improve the effectiveness of drug therapy and to reduce possible systematic side effects, many attempts have been made to deliver drugs in a controlled profile to human patients. The advantages of controlled release dosage forms are well known in both the pharmaceutical and medical sciences. The therapeutic benefits of controlled-release dosage forms include the pharmacokinetic ability to maintain a preplanned blood level of an administered drug over a comparatively longer period of time. The therapeutic benefits include also a simultaneous increase in patient compliance and a reduction in the number of doses of drug administered to a patient.

The prior art made available controlled release dosage that sought to provide a drug release rate profile that matched the blood physiological and chrono-pharmacological requirements needed for therapy. For example, an osmotic dosage form for delivering various drugs to a patient environment of use is presented in U.S. Pat. No. 3,845,770 issued to patentees Theeuwes and Higuchi, and in U.S. Pat. No. 3,916,899 issued to the same patentees. The dosage forms disclosed in these patents are manufactured comprising a wall that surrounds a compartment comprising a drug with an exit in the wall for delivering the drug to a patient. In U.S. Pat. Nos. 4,008,719; 4,014,334; 4,058,122; 4,116,241; and 4,160,452 patentees Theeuwes and Ayer made available dosage forms comprising an inside and an outside wall made of poly(cellulose acylate) for delivering a dosage of drug to a patient in need thereof.

Additional semipermeable polymers comprise acetaldehyde dimethylcellulose acetate; cellulose acetate ethylcarbamate; cellulose acetate methylcarbamate; cellulose diacetate propylcarbamate; cellulose acetate diethylaminoacetate; ethyl acrylate methyl methacrylate, semipermeable polyamide; semipermeable polyurethane; semipermeable sulfonated polystyrene; semipermeable crosslinked selective polymer formed by the coprecipation of a polyanion and polycation, as disclosed in U.S. Pat. Nos. 3,173,876; 3,276,586; 3,541,005; 3,541,006 and 3,546,876; semipermeable polymers as disclosed by Loeb and Sourirajan in U.S. Pat. No. 3,133,132; semipermeable, lightly crosslinked polystyrenes; semipermeable crosslinked poly (sodium styrene sulfonate); semipermeable crosslinked poly (vinylbenzyltrimethyl ammonium chloride); and semipermeable polymers possessing a fluid permeability in the range of 2.5.times.10.sup.-8 to 5.times.10.sup.-2 (cm.sup.2 /hr.multidot.atm), expressed per atmosphere of hydrostatic or osmotic pressure difference across the semipermeable exterior wall 12. The polymers are known to the polymer art in U.S. Pat. Nos. 3,845,770; 3,916,899 and 4,160,020; and in

Handbook of Common Polymers, by Scott, J. R. and Roff, W. J. 1971, CRC Press, Cleveland, Ohio. Wall 12, in a present manufacture can be coated from a substantially single solvent system, such as acetone if coated from a solution, or water if coated as a dispersion.

The present invention provides delivery of mifepristone, Compositions D1-D5 or other GRII antagonists (Drugs) via a sustained release or controlled release delivery techniques.

Effective Clinical Dosage for Mifepristone

Mifepristone [11β-(4dimethylaminophenyl)-17β-hydroxy-17-α-(propyl-1ynyl)-4,9-dien-3-one] is a glucocorticoid receptor antagonist with a molecular weight of 429.6 ($C_{29}H_{35}NO_2$). Several studies have reported on the daily oral administration of mifepristone (multiple dosing) (Croxatto et al., 1992, Foldesi et al., 1996, Heikinheimo et al. 1989, 1993, Kekkonen et al., 1996, Sakar, 2002, Swahn et al., 1986). The steady-state concentrations of mifepristone in the patient serum reported in these studies are compiled in Figure 1. In these clinical studies, the steady-state drug concentrations of 35-2300 ng/ml were achieve through daily doses of 1-200 mg (4-30 days).

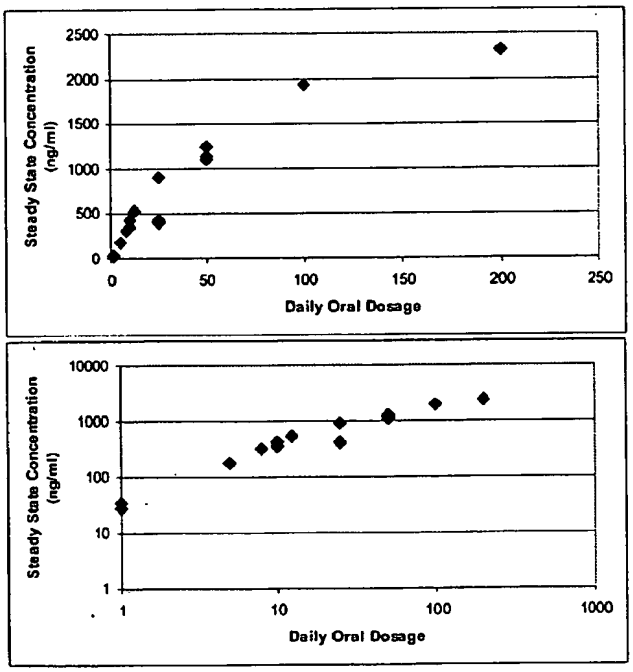

Figure 1: The steady-state concentration of mifepristone in the patient serum reported in published studies. In these clinical studies, the steady-state drug concentrations of 35-2300 ng/ml were achieve through daily doses of 1-200 mg.

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• Hydrogesterone
• Isopregnenone
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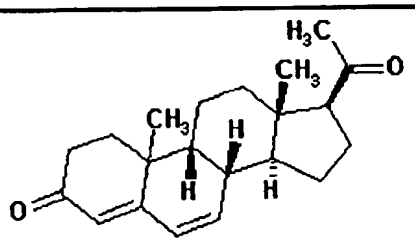
<tr><td colspan="3">  </td><td>Links to ChemID Plus by CAS#

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MDL Number: MFCD00199858.

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• Infecundin
• Norethinodrel
• Norethinynodrel
• Norethynodral
• Norethynodrel
• SC-4642
• WLN: L E5 B666OV MUTJ E1 F1UU1 QQ
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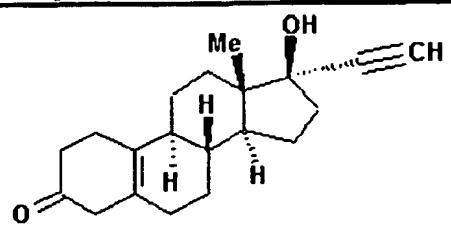
<tr><td colspan="3">  </td><td>Links to ChemID Plus by CAS#

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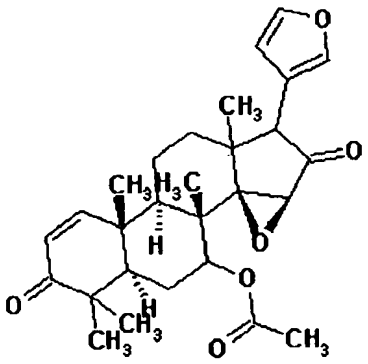			• Epoxyazadiradione • NSC640467		**Links to ChemID Plus by CAS#** 18385-59-6
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Company:			**Calc. LogP** (KowWin): 4.44		
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Classes: STEROIDS					

D4:

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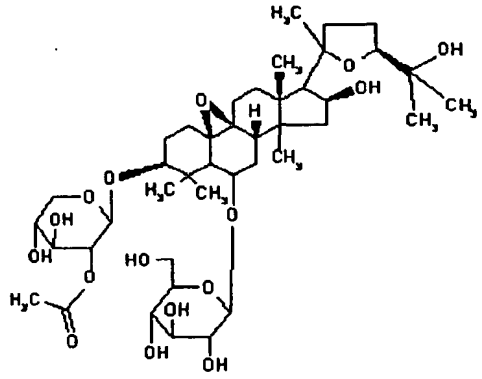
<tr><td colspan="3">  </td><td colspan="2"></td><td>Links to ChemID Plus by CAS#</td></tr>
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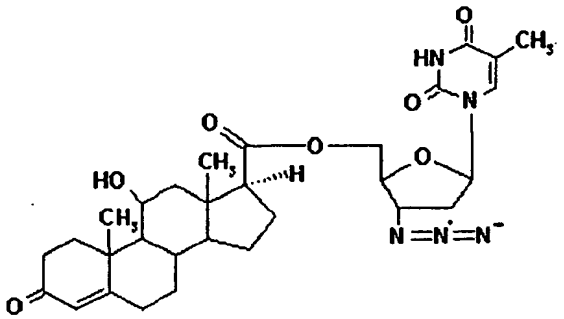
<tr><td colspan="3">Company:</td><td colspan="2">Calc. LogP (KowWin): -1.56</td><td></td></tr>
<tr><td>Lines of Data: 1</td><td>Anti-HIV Enzyme data: 0</td><td>Anti-OI data: 0</td><td>TB Min MIC</td><td>TB Min IC50</td><td rowspan="2"></td></tr>
<tr><td>Number of References: 1</td><td>Number of References: 0</td><td>Number of References: 0</td><td></td><td></td></tr>
<tr><td colspan="6">Classes: STEROIDS</td></tr>
</table>

D5:

Chemical Name: 3'Azido-3'deoxy-5'-O-[(11-.beta.-hydroxy-3-oxo-17-.beta.-androst-4-enyl)carbonyl]thymidine			**Synonyms** • AZT-5'-steroid ester		**AIDS#** 004495
					**Links to ChemID Plus by CAS#**
					Links to PubMed by CAS#
C30 H39 N5 O7		**MW:** 581.67			
H-bond donors: 2	**H-bond acceptors:** 12	**PHIA (Flexible Bonds):** 7.52	**Calc. LogP** (MDL QSAR): 2.15		
Company:			**Calc. LogP** (KowWin): -3.68		
Lines of Data: 1	Anti-HIV Enzyme data: 0	Anti-OI data: 0	**TB Min MIC**	**TB Min IC50**	
Number of References: 1	Number of References: 0	Number of References: 0			**Lipinsky:**
Classes: NUCLEOSIDES, PYRIMIDINE; PRODRUGS; CONJUGATES; NUCLEOSIDES, AZIDO; STEROIDS; AZT DERIVATIVES					

D5: Combination of Hydrocortisone Acetate and Zidovudine

Hydrocortisone Acetate Sigma Product Number: H4126
Zidovudine Sigma Product Number: 11546

	Compounds	References	
D6	pregnenolone 16-alpha - carbonitrile	Cell 1998, 92:73.	
D7	promegestrone	J Steriod Biochem 1988, 29:599	
D8	progesterone	J Steriod Biochem 1988, 29:600	Endocrinology 1980, 107: 118
D9	cortexolone	Endocrinology 1980, 107: 117	
D10	6-beta-bromogesterone	Endocrinology 1980, 107: 119	
D11	RU43044	PNAS 1992, 89:3571	
D12	RU40555	J Endcrinol. 2001, 169:309	
D13	spironolactone	Laryngoscope 2002, 112: 298	
D14	onapristone	Biol Pharm Bull 2002, 25: 1223	JBC 2000, 275: 17771
D15	cyproterone acetate	Mol Pharm 2003, 63:1012	
D16	trans 4-hydroxytamoxifen	JBC 2000, 275: 17771	
D17	RTI-3021-012	Endocrinology 1999, 140:1449	
D18	RTI-3021-022	Endocrinology 1999, 140:1450	

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference VGX0002-500	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2004/019756	International filing date *(day/month/year)* 21 June 2004 (21.06.2004)	Priority date *(day/month/year)* 20 June 2003 (20.06.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant VIRAL GENOMIX, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 13 March 2006 (13.03.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 740 14 35	Authorized officer Masashi Honda Telephone No. +41 22 338 70 10

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
MARK DELUCA
COZEN O'CONNOR
1900 MARKET STREET
PHILADELPHIA, PA 19103

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	19 DEC 2005
FOR FURTHER ACTION	See paragraph 2 below

Applicant's or agent's file reference		
VGX0002-500		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US04/19756	21 June 2004 (21.06.2004)	20 June 2003 (20.06.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A61K 1/56: A01N 43/04 and US Cl.: 514/49, 51; 435/5

Applicant

VIRAL GENOMIX, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450	03 October 2005 (03.10.2005)	Sreenivasan Padmanabhan, PhD
Facsimile No. (703) 305-3230		Telephone No. 703-308-1123

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/19756

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☐ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/19756

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-14	YES
	Claims 15-21	NO
Inventive step (IS)	Claims NONE	YES
	Claims 1-21	NO
Industrial applicability (IA)	Claims 1-21	YES
	Claims NONE	NO

2. Citations and explanations:

Claims 15-21 lack novelty under PCT Article 33(2) as being anticipated by Weiner et al US Patent 5,780,220.

The instant claims are directed to compositions comprising mifepristone and an antiviral such as acyclovir or ganciclovir.

Weiner discloses compositions comprising mifepristone and an antiviral such as acyclovir or ganciclovir and methods of use thereof in patients. (abstract, col 29-30). Thus, Weiner anticipates the limitations of the instant claims.

Claims 1-14 lack an inventive step under PCT Article 33(3) as being obvious over Weiner.

The teachings of Weiner are described above. Weiner fails to specifically administer his compositions to patients suffering from a coroovirus, picornovirus or flavivirus such as HCV, GB or JEV.

However, Weiner's compositions comprise many ingredients such compounds including acyclovir, ganciclovir etc that have been proved effective and approved by regulatory agencies for use for of treating various viral infections including HCV... Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to further use Weiner's compositions for treatment of such virus as HCV.

Claims 1-21 lack the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/19756

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/70;A01N 43/04
US CL : 514/49, 51; 435/5
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/49, 51; 435/5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,780,220 (WEINER et al) 14 July 1998 (07.07.1998), abstract, col 28, line 59-col 30, line 5.	15-21
Y		1-14
A	US 6,039,968 (NABAHI) 21 March 2000 (21.03.2000), abstract, col 8-11	1-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
03 October 2005 (03.10.2005)

Date of mailing of the international search report
19 DEC 2005

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Authorized officer
Sreenivasan Padmanabhan, PhD

Telephone No. 703-308-1123

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/19756

Continuation of B. FIELDS SEARCHED Item 3:
EAST. REGISTRY, CAPLUS

pestvirus, coronovirus, picornovirus, flavivirus, mifeprisone, acyclovir, gancivlovir, foscarnet

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 December 2004 (29.12.2004)

PCT

(10) International Publication Number
WO 2004/112720 A3

(51) International Patent Classification:
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(21) International Application Number:
PCT/US2004/019756

(22) International Filing Date: 21 June 2004 (21.06.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/480,499 20 June 2003 (20.06.2003) US

(71) Applicant *(for all designated States except US)*: **VIRAL GENOMIX, INC.** [US/US]; 450 Sentry Parkway E., Blue Bell, PA 19422 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **KIM, Jong, Joseph** [US/US]; 157 Orchard Drive, North Wales, PA 19454§ (US).

(74) Agent: **DELUCA, Mark**; Cozen O'Connor, 1900 Market Street, Philadelphia, PA 19103 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

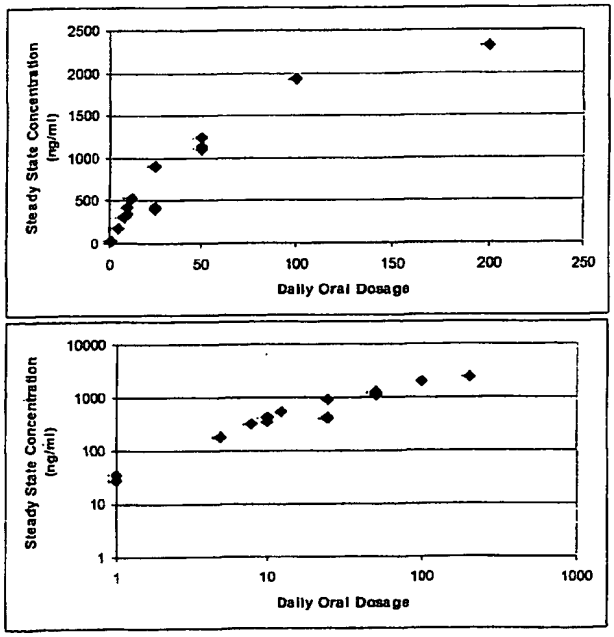
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

[Continued on next page]

(54) Title: ANTIVIRAL COMPOSITIONS AND METHODS OF USING THE SAME

(57) Abstract: Pharmaceutical compositions for and methods of preventing infection or treating an individual who has been identified as being infected with a Flavivirus, Pestivirus, picornovirus or coronavirus such as HCV, GB virus B, JEV, WNV, CSFV, BDV, BVDV, poliovirus, FMDV, or EMCV, comprising administering to the individual a therapeutically effective amount of one or more glucocorticoid receptor antagonist compounds, wherein said compound has steroidal structure are disclosed.



WO 2004/112720 A3

(88) Date of publication of the international search report:
30 November 2006

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.